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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/791,619	03/02/2004	Henry B. Lowman	P1123R1D1C1	4016

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EXAMINER

SZPERKA, MICHAEL EDWARD

ART UNIT	PAPER NUMBER
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1644

DATE MAILED: 06/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/791,619

Applicant(s)

LOWMAN ET AL.

Examiner

Michael Szperka

Art Unit

1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 29 April 2005.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 48-65 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 48-65 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 3/2/04.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

5-0-2

DETAILED ACTION

1. Applicant's response and amendments received April 29, 2005 are acknowledged.

Claim 48 has been amended.

Claims 48-65 are pending in the instant application.

Election/Restrictions

2. Applicant's election of the species food as an anaphylactic hypersensitivity allergen and the species food allergy as an IgE-mediated disorder in the reply filed on April 29, 2005 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the species election requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Upon the failure to find the elected species in the teachings of the prior art, the search of applicant's claimed method has been extended to additional allergen and disorder species.

Claims 48-65 are under examination in this office action.

Information Disclosure Statement

3. Applicant's IDS submitted March 2, 2004 is acknowledged and has been considered. Citation 17 has been considered but has been lined through because the

indicated document number is incorrect. The citation has been corrected and has been listed by the examiner on the form 892 that accompanies this office action.

Specification

4. Applicant has updated the first line of the specification in the preliminary amendment received March 2, 2004. This amendment fails to indicate the US patent number assigned to allowed parent application 09/716,028. Amendment of the specification to indicate that application 09/716,028 is US patent 6,723,833 is required.

The disclosure is objected to because of the following informalities:

- A. The conclusion statement found on lines 3 and 4 of page 79 appears inconsistent with the discussion of experiment VI on page 78 and the data presented in Figure 8. This experiment describes a competition assay wherein binding of anti-IgE antibodies to biotin labeled IgE prevents the biotin-labeled IgE from binding to the high affinity IgE receptor and being detected in the assay readout. The anti-IgE antibodies disclosed here and elsewhere throughout the specification are disclosed as binding IgE only, not the high affinity receptor. As such the statement on lines 3 and 4 of page 79 that "both E26 and E27 have greater affinity than E25 for the high affinity receptor" is puzzling since these antibodies do not bind the high affinity IgE receptor. Clarification is required.

- B. Line 22 of page 79 has a formatting error in that a box appears where presumably Applicant intended an apostrophe.

Appropriate correction of all of the above is required.

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 48-65 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of administering a humanized anti-IgE antibody, does not reasonably provide enablement for a method of administering an antibody or antigen-binding fragment comprising SEQ ID NOs: 8, 11, and 12 that treats anaphylaxis. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Applicant has claimed a method of administering an anti-IgE antibody or antigen-binding fragment thereof to treat IgE mediated disorders including anaphylaxis.

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Anaphylaxis is characterized by specific-antigen induced crosslinking of IgE bound to receptors found on the surface of mast cells and basophils, said crosslinking leading to degranulation and the release of soluble mediators including histamine and leukotrienes (Tortora et al., Microbiology, and Introduction, Fifth edition, (1995), pages 466-469, see entire selection). The reaction can be systemic or localized, with systemic reactions being characterized by a dangerous drop in blood pressure less than 30 minutes after exposure to the crosslinking antigen (see particularly Table 19.1 and page 468 of Tortora et al.). Such reactions are often seen after insect stings and must be treated promptly with epinephrine to prevent the death of the patient (see particularly the right column of page 468). The variable heavy and light chain sequences of the anti-IgE antibodies used in Applicant's claimed method are disclosed as binding to IgE in solution, but administering such an antibody after an anaphylactic reaction has started, such as after a bee sting, would do nothing to reverse the immediate drop in blood pressure and other physiological consequences mediated by the release of granule contents. Indeed, Chang (Nature Biotechnology, (2000) 18:157-162) teaches that it is unclear if administration of anti-IgE has any therapeutic benefit within the first days subsequent to administration (see entire document, particularly the last paragraph of the section titled *The downregulation of FcεRI* on page 161 which details the kinetics involved in the therapeutic administration of antibodies). As such, administration of antibodies to a patient currently suffering from an anaphylactic reaction would not yield a therapeutic benefit to the patient since IgE present on the surfaces of mast cells and basophils would already have been crosslinked by bound antigen and soluble mediators

would already have been released. Therefore it does not appear that Applicant's method can treat an ongoing anaphylactic reaction, something that is currently encompassed by the breadth of Applicant's claims.

It is possible that performing applicant's claimed method on a patient prior to the patient being exposed to the anaphylactic hypersensitivity allergen could potentially lessen the amount of soluble mediators released from mast cells and basophils and thus lessen the severity of the reaction. However, it is often difficult, if not impossible, for a patient to know when he will come in contact with a particular allergen, such as insect venom. As such it appears that anti-IgE would need to be administered prophylactically, since as discussed above, administration anti-IgE will not halt or reverse an anaphylactic reaction once it has begun. Anti-IgE antibodies persist in a patient's circulation for about a month at most (Chen, see particularly the last paragraph of the right column of page 159). As such, the antibodies administered in Applicant's method will have to be readministered on a routine basis (Chen, particularly the last paragraph of the left column of page 161). There is no indication in the claims that anti-IgE must be repeatedly administered to a patient.

The claims currently recite that the antibody or antigen binding fragments used in Applicant's method comprise specific variable heavy and light chain sequences, and the specification indicates that these sequences bind IgE and have been humanized. The comprising language allows these humanized sequences to be joined to addition sequence, for example Fc domains for whole antibodies or linker regions in making single chain antibodies. The additional sequence that can be added is not indicated as

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being human or humanized. It is well known in the art that repeated dosages of a therapeutic antibody can elicit an unwanted immune responses that neutralizes the therapeutic antibody (Kipriyanov et al., Molecular Biotechnology, (1999) 12:173-201, see entire document, particularly the first paragraph of the Introduction on page 173). This response is often referred to as HAMA (human antimurine antibody) since it was first seen using murine antibodies, but such reactions can occur with an antibody derived from any non-human animal. Strategies to reduce or eliminate the unwanted reaction of the patient's immune system to the administered antibody have been developed that humanize the antibody so that it is not recognized as foreign by the patient's immune response and therefore no neutralizing antibody response is generated by the patient's immune system (Kipriyanov et al., see particularly the second paragraph of the Introduction).

Applicant's method, as currently recited does not require the whole antibody or antigen binding fragment to be humanized. As discussed above, since administration of the anti-IgE antibody is not effective after exposure to antigen, and since, as is also discussed above, the timing of exposure to antigen cannot be predicted, the anti-IgE antibody needs to be repeatedly administered on a regular schedule. Unless the anti-IgE antibody is humanized, the patient will mount an immune response that neutralizes the anti-IgE antibody and Applicant's method will not work to treat any IgE-mediated disorder currently recited in the claims. Therefore a skilled artisan would be unable to use the full breadth of Applicant's claimed method of treating IgE-mediated disorders.

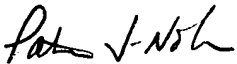
7. No claims are allowable.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Szperka whose telephone number is 571-272-2934. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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June 20, 2005


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